American Journal of Hematology 61:135–138 (1999)

Fatal Virus-Associated Hemophagocytic Syndrome Associated With Coexistent Chronic Active Hepatitis B and Acute Hepatitis C Virus Infection

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A 28-year-old man was admitted to our department with intermittent fever, hepatosplenomegaly and pancytopenia. Liver parameters and serum ferritin were markedly elevated. Bone marrow biopsy showed hypocellularity, histiocytic hyperplasia, and hemophagocytosis consistent with a virus-associated hemophagocytic syndrome (VAHS). There was serological evidence of chronic active hepatitis B and acute hepatitis C virus infection. The patient died despite aggressive immunosuppressive and supportive treatment. Autopsy revealed signs of acute viral hepatitis with cholestasis. Histiocytes engaged in hemophagocytosis were observed in bone marrow and spleen. The condition was interpreted as VAHS associated with chronic active hepatitis B and acute hepatitis C virus infection. To our knowledge this is the first report of a hemophagocytic syndrome in that setting. Am. J. Hematol. 61:135–138, 1999.

Key words: virus-associated hemophagocytic syndrome; hepatitis B virus; hepatitis C virus; treatment

INTRODUCTION

Virus-associated hemophagocytic syndrome (VAHS) is a rare and often fatal disorder characterized by fever, splenomegaly, peripheral cytopenia, and benign proliferation of hemophagocytic histiocytes in the reticuloendothelial system [1]. VAHS has been reported in association with many different viruses including Epstein-Barr virus (EBV) [2], cytomegalovirus (CMV) [3], varicella-zoster virus (VZV) [4], herpes simplex virus (HSV) [1], parvovirus B19 [5], adenovirus [6], coxsackie virus [7], human immunodeficiency virus (HIV) [8], hepatitis A virus (HAV) and hepatitis C virus (HCV) [9]. The syndrome can occur in both immunosuppressed and previously healthy individuals [1]. Patients with VAHS typically present with fever and splenomegaly [10]. Hepatomegaly is a common finding, while lymphadenopathy and skin rash occur less frequently [1]. Laboratory findings include peripheral blood cytopenia, impaired liver function, coagulopathy, hypofibrinogenemia, hypertriglyceridemia, and hyperferritinemia [10]. Bone marrow findings include histiocytic hyperplasia, hemophagocytosis, and hypocellularity [1]. The clinical course of VAHS is highly variable and spontaneous remission is sometimes seen [1,5]. In many cases, though, VAHS is a dramatic illness with fatal outcome. Death is typically caused by septicemia, coagulopathy and multiorgan failure [11,12]. In this article a case of VAHS associated with coexistent chronic active hepatitis B virus (HBV) and acute HCV infection is described, and the treatment of the disease is discussed.

CASE REPORT

A 28-year-old African male was admitted to our department on suspicion of acute leukemia. Allegedly he was in good health until two weeks before admission, when he developed intermittent fever with temperature

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Received for publication 28 July 1998; Accepted 6 January 1999

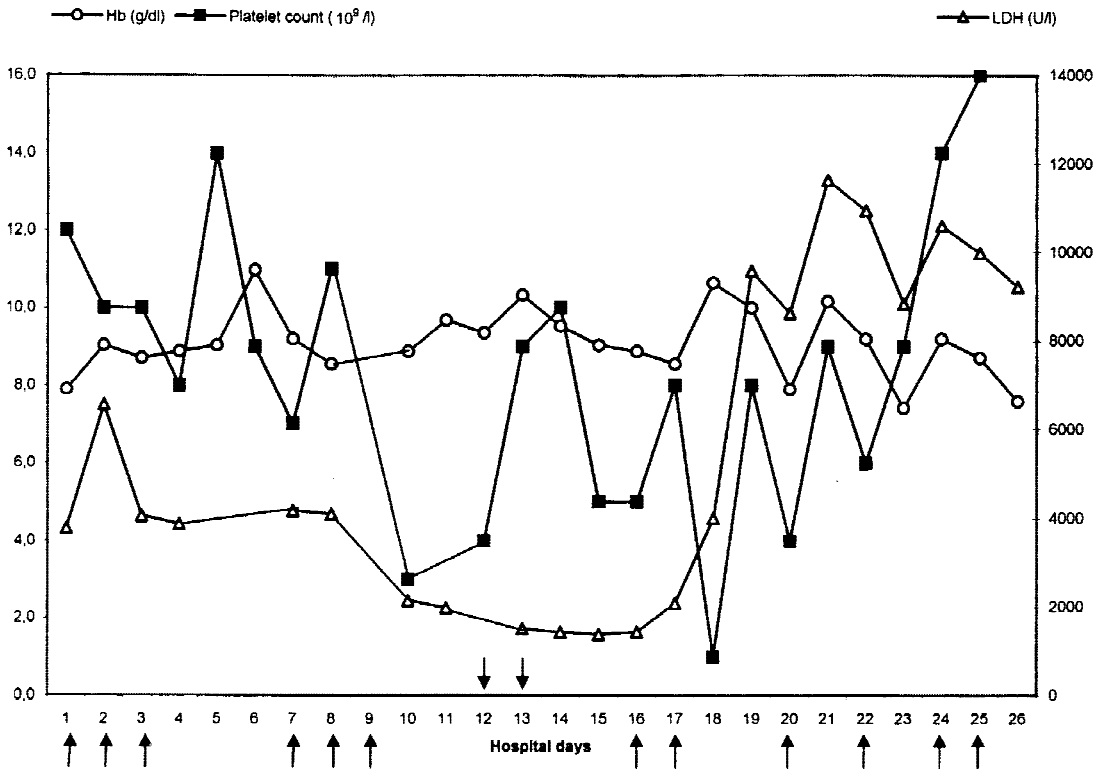

Fig. 1. Development in hematological parameters and serum lactate dehydrogenase from hospital day 1 to 26. Hemoglobin level (Hb): normal 12.9–17.7 g/dl. Platelet count: normal 150–400 × 10^9/l. Serum lactate dehydrogenase (LDH): normal 150–450 U/l. Arrows indicate transfusion of red blood cells and/or platelets.

up to 39°C. The patient was born and raised in Ghana and had been living in Denmark for 10 years. There was no history of intravenous drug abuse. Clinical investigation revealed hepatosplenomegaly. Initial laboratory results (day 1) included a hemoglobin of 7.9 g/dl (normal 12.9–17.7), a platelet count of 12 × 10^9/l (150–400) and a leukocyte count of 0.5 × 10^9/l (3.0–9.0). Serum ferritin was heavily increased to 22.533 μg/l (19–323). Liver function studies showed alanine aminotransferase 326 U/l (10–40), aspartate aminotransferase 268 U/l (10–40), alkaline phosphatase 426 U/l (80–275) and lactate dehydrogenase (LDH) 3.780 U/l (150–450). The coagulation factors II-VII-X were 0.51 U/l (0.7–1.3). The development in hematological parameters and serum LDH is shown in Figure 1. Bone marrow biopsies (day 1 and day 3) revealed a hypoplastic bone marrow with dysplastic red precursor cells, sparse megakaryocytes, markedly reduced myelopoiesis and an increased number of well-differentiated macrophages containing phagocytosed red blood cells (Figure 2). Chromosome analysis showed a normal karyotype. Sections of the bone marrow were stained for parvovirus, HSV I and II, CMV and EBV with negative results, and a polymerase chain reaction investigation for *Mycobacterium tuberculosis* was also negative. The bone marrow changes were not representative for malignant histiocytosis but consistent with a hemophagocytic syndrome.

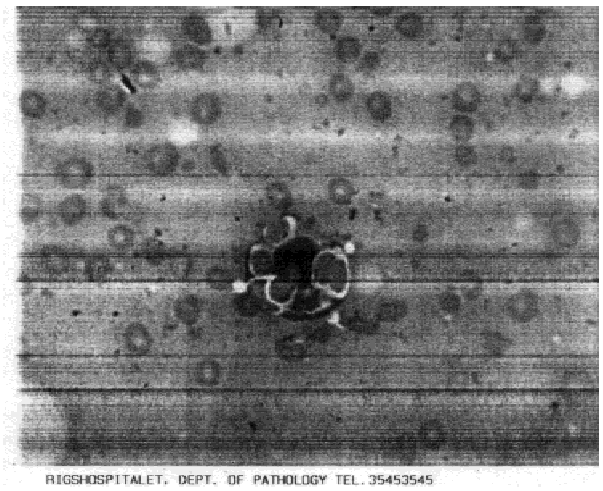

Fig. 2. VAHS. Bone marrow: a well-differentiated macrophage containing phagocytosed red blood cells (original magnification ×400).

On suspicion of VAHS treatment with methylprednisolone 80 mg i.v. × 3 daily, cyclosporin 75 mg i.v. × 2 daily and granulocyte colony-stimulating factor (G-CSF) 600 μg s.c. × 1 daily was started on day 7 without documented viral infection.

There was serological evidence of previous infections with CMV, EBV, HAV and Toxoplasma gondii. No an-

tibodies to HIV, parvovirus B19, influenzavirus, adenovirus, respiratory syncytial virus, *Mycoplasma pneumoniae* or *Legionella pneumophila* were found. HBV studies showed that the patient was anti-HBs antibody negative, HBsAg positive anti-HBc IgM negative, anti-HBc total antibody positive and HBV-DNA positive consistent with chronic active HBV infection (results from day 10 to 21). The patient was HCV antibody negative but HCV-RNA positive (day 13), compatible with active HCV infection in an immunosuppressed individual unable to raise antibodies toward the virus or simply acute HCV infection. As the leukocyte count never exceeded $0{,}7 \times 10^9$/l, both of these interpretations seemed probable. AMPLICOR HCV detection kit, ROCHE, was used for detection of HCV-RNA, and HCV antibody investigation was carried out using ORTHO HCV 3.0 ELISA test system, ORTHO.

The condition was interpreted as a virus-associated hemophagocytic syndrome associated with coexistent chronic active HBV infection and acute HCV infection. Risk factors for contraction of HBV/HCV were not identified, perhaps because of a considerable language barrier. Immunosuppressive treatment was continued and for five days supplemented with i.v. gamma-globulin therapy (from day 17 to 21).

During weeks 2 and 3 the patient's condition deteriorated rapidly. Temperature was constantly high (39–40°C), and the kidney function steadily declined. A bone marrow biopsy on the sixteenth hospital day showed persistent hypocellularity, histiocytic, hyperplasia and hemophagocytosis. Treatment with antithymocyt-globulin (ATG) was started on day 23. Three days later the patient developed cardiac arrest during insertion of a central venous catheter and died despite intensive resuscitation attempts.

Autopsy Findings

Autopsy revealed splenomegaly and a yellowish brown, slightly enlarged liver. The liver showed microscopic signs of acute viral hepatitis with cholestasis. Hepatocytes varied in size and stained positive for HBsAg. Portal tracts were without lymphocytic infiltration or piecemeal necroses. The lack of inflammatory reaction was ascribed to the immunosuppressed status of the patient. In the spleen and bone marrow histiocytes and hemophagocytosis was observed.

DISCUSSION

Table I shows diagnostic criteria for VAHS and other infection-related hemophagocytic syndromes [13]. Some authors use slightly modified criteria [10,11]. The pathogenesis of VAHS is poorly understood, but may involve an abnormal, uncontrolled T helper cell-mediated immune response to virus infection [11]. Serum-levels of INF-γ, IL-1, IL-2, IL-6, TNF-α, IL-2-R, M-CSF, plasminogen activator, and various prostaglandins are often elevated in patients with VAHS [14–17]. Many authors suggest that virus infection provokes hypersecretion of IL-2, IFN-γ and M-CSF from activated Th1 cells. Stimulated by these cytokines macrophages proliferate, engage in hemophagocytosis and release IL-1, IL-6, TNF-α and ferritin. The resultant hypercytokinemia is assumed to be responsible for the clinical and biochemical manifestations of VAHS: fever, bone marrow suppression, immunodeficiency, hyperferritinemia, hyperlipidemia, hypofibrinogenemia, and disseminated intravascular coagulation [11,14,18].

TABLE I. Diagnostic Criteria for the Infection-Related Hemophagocytic Syndromes [13]

Fever (38, 5°C or higher at presentation)
Splenomegaly
Plus two of the following hematological abnormalities:
■ Anemia <9 g/dl hemoglobin
■ Thrombocytopenia $<100 \times 10^9$ platelets/l
■ Neutropenia $<1.0 \times 10^9$ neutrophils/l
Hypofibrinogenemia
Hemophagocytosis: moderate to marked involvement in at least two of the following sites: lymph node, liver, spleen, bone marrow
No evidence of primary immunodeficiency, hypoplastic bone marrow, or malignant neoplasia

The literature does not provide clear answers as to how VAHS should be treated. In some reports complete remissions have been accomplished on supportive treatment with antibiotics and blood components only [1,5], while in other investigations symptomatic treatment was insufficient [4,9]. In the setting of EBV-associated hemophagocytic syndrome supportive treatment in combination with acyclovir has been given with curative result in one trial [2]. In another study six patients with EBV-associated hemophagocytic syndrome were unsuccessfully treated with antiviral, immunosuppressive, and cytotoxic agents [12]. Complete clinical remissions have been described after treatment with etoposide [14,19], and intravenous immunoglobulin therapy has improved the prognosis of patients with VAHS in several cases [20,21]. Recently, cyclosporin in combination with G-CSF was administered to four adult patients with VAHS [11]. All patients achieved complete clinical and biochemical remission.

In childhood cases of VAHS the fatality rate seems to be particularly high [22]. A treatment protocol for children aged 15 years or less with hemophagocytic lymphohistiocytosis (including children with VAHS) has been developed by the Histiocytic Society [23]. In this protocol therapy consisting of etoposide, dexamethasone and cyclosporine followed by BMT is recommended. A similar protocol for treatment of adult patients with VAHS does not exist. The demise of our patient clearly demonstrates that immunosuppressive treatment is inadequate

in some cases of adult VAHS. Therefore, adult patients who do not respond satisfactory to treatment with cyclosporin and high-dose immunoglobulin in combination with antibiotics, blood components and G-CSF [2,4,11,20], should probably be quickly changed to the more aggressive dexamethasone/etoposide/cyclosporine/BMT-protocol of the Histiocytic Society [23].

In this article a case of fatal VAHS associated with coexistent chronic active HBV and acute HCV infection has been described. To our knowledge VAHS has never been reported in that setting before.

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